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Title: Basal Cell Carcinoma: Management of Advanced or Metastatic Cancer with Checkpoint Inhibitors and Concurrent Paradoxical Development of New Superficial Tumors

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BCC&PD-1/PD-L1 JAAD Accepted Letter to Editor Feb 2020

To the Editor:

Choi et al provided a comprehensive review of programmed cell death 1 protein (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors in the treatment of nonmelanoma skin cancer.[1] However, they incorrectly commented that the new primary cutaneous superficial basal cell carcinomas (BCCs) that paradoxically developed in our patient with metastatic BCC also responded to nivolumab.[2-4] We want to emphasize this important observation, since it provides additional insight into the mechanism of therapeutic benefit and limitations when immunotherapy is considered for patients with metastatic BCC, and to share the features of additional patients with advanced or metastatic BCC who were treated with checkpoint inhibitors.[4,5]

The first patient, a 58-year-old man, developed new primary cutaneous BCCs nine months after initiating nivolumab and achieving near complete remission of his widely metastatic BCC. His metastatic tumor had been refractory to treatment with chemotherapy (cisplatin and paclitaxel) and Hedgehog pathway inhibitors (vismodegib and sonidegib; the latter was combined with buparlisib, a pan-class I PIK3 inhibitor). Next generation sequencing (NGS) of his liver metastasis not only demonstrated multiple genomic alterations (including PD-L1 amplification), but also a tumor mutational burden (TMB) of 103 mutations per megabase (m/mb); $\geq$20 m/mb is considered to be a high

TMB and associated with better responses to immunotherapy. In contrast, the new primary cutaneous BCCs had fewer genomic alterations, did not exhibit PD-L1 amplification, and had a lower TMB of 45 m/mb.[2-4,6]

The second patient, a 62-year-old man, presented with an advanced BCC on his upper back (Figure 1a). NGS of his tumor demonstrated 11 significant genomic variants and a high TMB (53 m/mb). He was treated with vismodegib and nivolumab. He achieved complete remission after five months of treatment. Vismodegib was stopped after 8.5 months. He continues to remain in remission more than 12 months after stopping therapy (Figure 1b).[4,5]

The third patient, a 53-year-old woman, had metastatic BCC. NGS of her cutaneous and metastatic tumor demonstrated six and 12 genomic alterations, respectively; both tumors had a high TMB (90 m/mb). She achieved partial remissions with vismodegib and subsequently nivolumab; however, her progression free survival was only 4.5 months and 3.8 months, respectively.[4]

The fourth patient, a 50-year-old woman, had metastatic BCC; NGS demonstrated ten genomic alterations and a TMB of 102 m/mb. Vismodegib resulted in a partial remission lasting 11.1 months; progressive disease occurred 2.5 months after starting pembrolizumab.[4]

In summary, we propose that checkpoint inhibitors may be more successful in patients with ‘late’ metastatic disease in which the tumor has more genomic aberrations and high TMB. In contrast, treatment with targeted therapies such as vismodegib (or excision for localized disease) may be better for patients with genomically less complex BCCs. In our patient, the paradoxical development of new superficial cutaneous BCC—in the setting of concurrently receiving immunotherapy and achieving near complete remission of his metastatic BCC—occurred since the checkpoint inhibitor was not able to prevent his ‘early’ neoplastic disease that was characterized by fewer molecular alterations and a lower TMB.

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Legend

Figure 1 (a and b). An advanced BCC (10 x 8 x 2.5 cm) without metastatic disease on the upper back of a 62-year-old man (a); the erythema on his back surrounding the tumor was caused by allergic contact dermatitis to band aid adhesive. He was treated concurrently with four total intravenous doses of nivolumab (240 mg for three doses and 120 mg for the final dose) and oral vismodegib (150 mg daily); the nivolumab was discontinued because of steroid-responsive grade three skin rash and recurrent transaminitis. After five months of treatment, he achieved a complete and sustained remission; multiple skin biopsies showed no evidence of disease. The vismodegib was stopped after 8.5 months secondary to loss of appetite in the setting of complete remission. There is no recurrence at follow up nine months after stopping treatment (b).